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Original Article

# Evaluation of the impact of nutritional parameters on mortality in patients with multiple myeloma

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## ABSTRACT

**Aims:** Multiple myeloma (MM) is a type of cancer originating in plasma cells. While it can be managed with treatment, it is typically not curable. Recent research has underscored the significance of nutritional factors in forecasting the prognosis of patients with MM. This study aims to investigate the impact of nutritional indicators on mortality among patients diagnosed with multiple myeloma.

**Methods:** We performed a retrospective study to analyze overall survival (OS) in 225 patients with MM, focusing on the association between the controlling nutritional status (CONUT) score, the Geriatric Nutritional Risk Index (GNRI), and patient outcomes.

**Results:** Of the patients, 69 (30.7%) were younger than 65, while 156 (69.3%) were aged 65 years or older. The impact of CONUT scores on OS was statistically significant, particularly in patients aged 65 years and older (p=0.042). Among patients who had undergone autologous peripheral blood stem cell transplantation (Auto-PBSCT), a statistically significant correlation was observed between GNRI scores and survival times (p=0.002). Our results suggest improving patients' nutritional status positively influences treatment outcomes and survival rates.

**Conclusion:** The efficacy of nutritional scores on survival in MM has been demonstrated. We recommend clinicians assess patients' nutritional status when developing treatment plans and consider implementing appropriate nutritional interventions.

**Keywords:** CONUT, GNRI, multiple myeloma, nutritional, overall survival

## INTRODUCTION

Multiple myeloma (MM) is a blood malignancy characterized by the excessive proliferation of atypical plasma cells in the bone marrow. It stands as the second most prevalent hematologic cancer after lymphoma, representing roughly 1% of all cancers and approximately 10% of hematologic malignancies.[1] The median age at diagnosis is 65 years, with less than 3% of patients being younger than 40 years old.[2] The disease progression, treatment processes, and patients' quality of life are significantly influenced by nutritional factors. In this article, we aim to evaluate the impact of nutritional parameters, particularly on mortality, in patients with MM. In patients with MM, advanced age at diagnosis and treatment-related complications variably affect OS. Inadequate nutritional status has been linked to reduced response to chemotherapy and a higher risk of treatment-related complications, both of which can negatively affect the overall prognosis in individuals with cancer.[3] When assessing performance status and frailty in patients with various cancer types, nutritional status indicators such as CONUT, Prognostic Nutritional Index (PNI), and the Geriatric Nutritional Risk Index (GNRI) provide valuable insights. Studies have demonstrated the importance of evaluating these measurements to manage chemotherapy response and toxicities.[4-9]

The CONUT score is calculated using total cholesterol, serum albumin, and lymphocyte count. This scoring system reflects patients' immune and nutritional statuses. Due to the simplicity of obtaining and calculating the parameters used in the CONUT score, it has been widely employed in recent studies for evaluating patients' nutritional statuses. Patients receive scores based on specified laboratory parameters in the CONUT scoring system, with the total score indicating the patient's CONUT score. CONUT score primarily assesses patients' nutritional status and has gained prominence recently. It was initially introduced to predict prognosis by evaluating postoperative complications and mortality among hospitalized patients, particularly those undergoing gastrointestinal surgery.[10] Recent studies have shown that the CONUT scoring system effectively predicts prognosis in certain malignancies and chronic diseases.[11,12] In this scoring system, albumin, a crucial parameter for evaluating nutritional status and inflammation, has the most significant

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impact. Additionally, lymphocyte count is considered an indicator of immune system function, and low levels of cholesterol have been noted to correlate with poor prognosis in malignant diseases.[11] Accordingly, these findings suggest that the CONUT score can be utilized to monitor patients' nutritional status and predict prognosis and mortality in chronic and malignant diseases.

The GNRI is a tool commonly used to assess nutritional risk, particularly in older adults. Research has demonstrated that GNRI is associated with a range of clinical outcomes. Higher GNRI scores in elderly patients with acute respiratory failure have been linked to lower hospital mortality rates and shorter hospital stays.[13] The GNRI is an important screening tool that assesses nutritional risk calculated by serum albumin level and ideal body weight.[14]

The GNRI was initially employed in 2005 to assess the relationship between malnutrition and mortality among elderly patients hospitalized. This index also can predict potential complications caused by inadequate nutrition.[15] GNRI was developed to predict the risk of morbidity and mortality due to malnutrition in the elderly population and is associated with poor outcomes linked to various diseases, including cancer. The GNRI score requires evaluating serum albumin levels and calculating ideal body weight using the Lorentz formula. The score is computed using the following equation.[14-19]

The GNRI has become a valuable predictor of outcomes across various malignancies, including hematologic and gastrointestinal cancers. Meta-analyses indicate that a low GNRI is associated with unfavorable OS, progression-free survival, and disease-free survival in patients with hematologic malignancies.[20,21] In conditions such as myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes, a low GNRI predicts early mortality and shorter OS among patients treated with azacitidine.[22] Similarly, in gastrointestinal cancers, a low GNRI is linked to increased postoperative complications and poorer long-term outcomes.[23] The prognostic value of GNRI appears consistent across different cancer types and treatment approaches, underscoring its potential as a straightforward yet effective tool for assessing nutritional risk and predicting adverse outcomes in cancer patients.[21] This study evaluated the effect of GNRI and CONUT scores on response to treatment and OS in patients with MM.

## METHODS

### Patients and Treatments

Between 2013 and 2023, a total of 225 individuals diagnosed with symptomatic multiple myeloma (MM) at Sivas Cumhuriyet University Faculty of Medicine (Sivas, Turkiye) were retrospectively evaluated in this study. The final follow-up was conducted in May 2024. Information regarding patient demographics and clinical features was collected from institutional medical records and the hospital database. Approval was received for this retrospective study from the Sivas Cumhuriyet University Non-interventional Clinical Researches Ethics Committee (Date: 18.01.2024, Decision No: 2024-01/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### CONUT Score

The CONUT score, which is calculated using serum albumin, total lymphocyte count, and total cholesterol levels, is an effective method for the early assessment of nutritional deficiencies. Based on the score, patients are classified into four nutritional status groups: normal (0-1), mild malnutrition (2-4), moderate malnutrition (5-8), and severe malnutrition (9-12).[25]

### GNRI Score

The GNRI, introduced by Bouillanne et al.[14] in 2005, is a straightforward and reliable tool for assessing nutritional status. It evaluates nutritional risk by considering serum albumin levels and the ratio of current body weight to ideal body weight. The GNRI calculation formula is as follows:

GNRI=1.489×albumin (g/L)+41.7×ideal weight current weight

Ideal weight is calculated using the Lorentz formula:

- For males: Height (cm)-100-[(Height (cm)-150)/4]
- For females: Height (cm)-100-[(Height (cm)-150)/2.5]

The GNRI value serves as a tool used by healthcare professionals, typically in geriatric populations, to evaluate the nutritional status of patients.[14] According to GNRI scores, the GNRI is categorized into four layers based on nutritional risk (Q1-Q4): Q1 represents a major-risk layer with GNRI<82; Q2 signifies a moderate-risk layer with 82≤GNRI<92; Q3 indicates a low-risk layer with 92≤GNRI≤98; and Q4 denotes a no-risk layer with GNRI>98.[26]

### Statistical Analysis

The data collected during the study were analyzed using the IBM SPSS software, version 26.0. The normality of the measurements was assessed using the Kolmogorov-Smirnov test, and descriptive statistics, including minimum, maximum, mean, standard deviation, median, and $25^{th}$-$75^{th}$ percentile values, were presented. For variables meeting the assumptions of parametric tests, one-way ANOVA was used for comparisons involving more than two groups. The Kruskal-Wallis H test was preferred for continuous variables with unmet parametric test assumptions. In cases where measurements followed a normal distribution, if the statistical difference between group means was significant in comparisons involving more than two groups, the LSD test was used to determine the differentiation between group means for homogeneous data, and Tamhane's T2 test was applied for non-homogeneous data. The Mann-Whitney U test compared two groups with non-normally distributed data. Survival rates in the disease were calculated using the Kaplan-Meier method and compared using the log-rank test. A significance level of $p<0.05$ was accepted; however, Bonferroni correction was applied for multiple comparisons to control the type I error.

## RESULTS

A total of 225 newly diagnosed multiple myeloma (MM) patients were enrolled in the study, including 87 females (38.7%) and 138 males (61.3%). The age distribution of the patients was as follows: 69 patients (30.7%) were younger than 65 years old, and 156 patients (69.3%) were 65 years or older.

In the first-line treatment, patients received Bortezomib + Cyclophosphamide + Dexamethasone (68.4%), Vincristine + Adriamycin + Dexamethasone (14.2%), Melphalan + Prednisolone (5.3%), Bortezomib + Dexamethasone (4.4%), Bortezomib + Dexamethasone (1.8%), and lenalidomide + Dexamethasone (0.4%). Twelve patients (5.3%) were managed with observation without treatment. The response rate to first-line treatment was 40.9%, and the non-response rate was 53.8%. 60 patients (26.7%) underwent autologous stem cell transplantation (ASCT) following first-line treatment.

In the second-line treatment, lenalidomide + Dexamethasone (30.2%), Bortezomib + Cyclophosphamide + Dexamethasone (15.6%), Bortezomib (1.8%), Bortezomib + Dexamethasone (1.3%), and Bortezomib + Lenalidomide + Dexamethasone (0.4%) protocols were administered to a total of 111 patients. Forty-eight patients (21.3%) achieved a response, and 21 patients (9.3%) underwent ASCT following second-line treatment.

Third-line treatment included lenalidomide + Dexamethasone (11.1%), Bortezomib + Cyclophosphamide + Dexamethasone (6.2%), Daratumumab + lenalidomide + Dexamethasone (1.3%), Bortezomib (0.9%), Melphalan + Prednisolone (0.4%), Pomalidomide + Dexamethasone (0.4%), and VTD-PACE (0.4%) protocols administered to 47 patients. Nineteen patients (8.4%) achieved a response, and 7 patients (3.1%) underwent ASCT, while 2 patients (0.9%) received allogeneic stem cell transplantation (allo-SCT) following third-line treatment.

In the fourth-line treatment, lenalidomide + Dexamethasone (8.0%), Bortezomib + Cyclophosphamide + Dexamethasone (0.4%), and Bortezomib (0.4%) protocols were administered to 20 patients. Eight patients (3.6%) achieved a response, although none underwent stem cell transplantation. Table 1 presents the patients' anthropometric distributions. Table 2 and 3 present the distribution of patients' laboratory findings at the time of diagnosis according to CONUT and GNRI scores, respectively. A reduced response to first-line therapy was noted in individuals with moderate to high CONUT scores. As shown in Table 4, there was no statistically significant relationship between the CONUT score and the response to second- and third-line treatments. A lower response to first-line treatment has been observed in patients categorized as moderate/severe risk based on GNRI score. Table 5 shows that no statistically significant relationship was observed between GNRI scores and the response to second- and third-line treatments.

**Table 1. Anthropometric distributions of patients**

| | | |
|---|---|---|
| **Height X±SD** | 163.40±10.14 | |
| **Weight X±SD** | 73.03±13.02 | |
| **Age** | **Number (n)** | **Percent (%)** |
| <65 | 69 | 30.7 |
| ≥65 | 156 | 69.3 |
| **CONUT** | **Number (n)** | **Percent (%)** |
| Normal | 51 | 22.7 |
| Mild | 97 | 43.1 |
| Moderate | 66 | 29.3 |
| Severe | 11 | 4.9 |
| **GNRI** | **Number (n)** | **Percent (%)** |
| Severe risk | 32 | 14.2 |
| Moderate risk | 30 | 13.3 |
| Low risk | 31 | 13.8 |
| No risk | 132 | 58.7 |

SD: Standard deviation, CONUT: Controlling nutritional status, GNRI: Geriatric Nutritional Risk Index

**Table 2. Distribution of laboratory measurements of patients according to CONUT scores**

| | CONUT | | | | |
|---|---|---|---|---|---|
| | **Normal** | **Mild** | **Moderate** | **Severe** | **p** |
| Chol (mg/dl) | 199.13±43.73 | 148.87±45.97 | 133.19±47.28 | 101.18±31.60 | .000* |
| Cre (mg/dl) | .99(.74-1.3) | .95(.75-1.51) | 1.15(.84-1.84) | 1.08(.80-2.1) | .181 |
| Albumin (g/L) | 4.1(3.74-4.51) | 3.53(3.25-4.16) | 2.93(2.6-3.1) | 2.39(2.3-2.84) | .000* |
| WBC ($10^9$/L) | 6.87(5.52-8.17) | 6.07(4.68-8.04) | 5.34(4.097-7.425) | 5.1(3.91-7.02) | .040* |
| Neu ($10^9$/L) | 3.73(3.08-5.28) | 3.54(2.78-5.13) | 3.06(2.38-4.75) | 3.50(2.00-4.70) | .274 |
| Lymp ($10^9$/L) | 2.00(1.66-2.43) | 1.66(1.28-2.30) | 1.235(0.95-2.298) | 0.8(0.32-0.98) | .000* |
| Hgb (g/dl) | 11.7(10-13.1) | 10.5(9.5-11.85) | 10.05(8.7-11.27) | 10.3(8.1-11.1) | .001* |
| Plt ($10^9$/L) | 221.60±105.10 | 203.49±99.92 | 204.98±109.91 | 133.54±62.42 | .087 |

*p<0.05, CONUT: Controlling nutritional status, Chol: Cholesterol, Cre: Creatine, WBC: White Blood Cell, Neu: Neutrophil, Lmph: Lymphocyte, Hgb: Hemoglobin, Plt: Platelet

**Table 3. Distribution of basic patient characteristics according to GNRI scores**

| | GNRI | | | | |
|---|---|---|---|---|---|
| | **Severe** | **Moderate** | **Low risk** | **No risk** | **p** |
| Chol (mg/dl) | 118±35.95 | 146.6±52.03 | 166.00±57.42 | 160.46±51.61 | .000* |
| Cre (mg/dl) | .95 (.79-1.55) | 1.36 (.98-2.38) | 1.10(.83-1.56) | .97(.74-1.43) | .034* |
| Albumin (g/L) | 3 (2.39-3.3) | 2.87 (2.6-3.23) | 3.20(2.89-3.51) | 3.90(3.4-4.3) | .000* |
| WBC ($10^9$/L) | 6.82 (4.48-8.65) | 5.68 (4.10-8.94) | 5.50(4.16-7.81) | 6.16(4.77-7.77) | .786 |
| Neu ($10^9$/L) | 4.66 (2.80-5.66) | 3.35 (2.29-6.03) | 3.28(2.72-4.28) | 3.50(2.61-5.01) | .420 |
| Lymp($10^9$/L) | 1.17(0.97-1.64) | 1.54 (1.11-2.22) | 1.68(0.96-2.53) | 1.77(1.25-2.40) | .018* |
| Hgb (g/dl) | 10.2 (9.25-1.65) | 9.65 (9.2-11.1) | 10.8(9.1-12) | 10.55(9.6-12.4) | .195 |
| Plt ($10^9$/L) | 241.97±131.59 | 168.76±68.35 | 153.33±82.459 | 215.76±101.44 | .001* |

*p<0.05, GNRI: Geriatric Nutritional Risk Index, Chol: Cholesterol, Cre: Creatine, WBC: White Blood Cell, Neu: Neutrophil, Lmph: Lymphocyte Hgb: Hemoglobin, Plt: Platelet,

**Table 4. Relationship between patients' response to treatment and CONUT score**

| | | CONUT | | | | |
|---|---|---|---|---|---|---|
| | | Normal n (%) | Mild n (%) | Moderate n (%) | Severe n (%) | Test/p |
| First-line treatment | No response | 21(42.9) | 44(47.8) | 49 (80.3) | 7 (63.6) | $X^2$=20.873/.000* |
| | Response | 28 (57.1) | 48 (52.2) | 12 (19.7) | 4 (36.4) | |
| Second-line treatment | No response | 17 (60.7) | 24 (50.0) | 18 (62.1) | 4 (66.7) | $X^2$=1.645/.649 |
| | Response | 11 (39.3) | 24 (50.0) | 11 (37.9) | 2 (33.3) | |
| Third-line treatment | No response | 8 (28.6) | 10 (35.7) | 7 (25.0) | 3 (10.7) | LR=.892/.832 |
| | Response | 5 (26.3) | 9 (47.4) | 4 (21.1) | 1 (5.3) | |

CONUT: Controlling nutritional status

**Table 5. Relationship between patients' response to treatment and GNRI score**

| | | GNRI | | | | |
|---|---|---|---|---|---|---|
| | | Severe risk n (%) | Moderate risk n (%) | Low risk n (%) | No risk n (%) | Test/p |
| First-line treatment | No response | 25 (78.1) | 20 (71.4) | 16 (51.6) | 60 (49.2) | $X^2$=11.600/.009* |
| | Response | 7 (21.9) | 8 (28.6) | 15 (48.4) | 62 (50.8) | |
| Second-line treatment | No response | 11 (50.0) | 7 (63.6) | 8 (80.0) | 37 (54.4) | $X^2$=2.975/.396 |
| | Response | 11 (50.0) | 4 (36.4) | 2 (20.0) | 31 (45.6) | |
| Third-line treatment | No response | 5 (55.6) | 2 (50.0) | 2 (66.7) | 19 (61.3) | LR=.311/.958 |
| | Response | 4 (44.4) | 2 (50.0) | 1 (33.3) | 12 (38.7) | |

GNRI: Geriatric Nutritional Risk Index

Significant effects of CONUT scores on OS in patients aged 65 years and older were found. No statistically significant relationship was observed between CONUT score and survival durations in patients under 65 (**Figure A**). Elderly patients with severe CONUT levels had shorter survival than those with normal, mild, and moderate levels (**Figure B**). Across all age groups, there was no statistically significant association between GNRI scores and survival durations (**Figure C and D**). Among patients without a history of Auto-PBSCT, a statistically significant relationship was found between CONUT scores and survival durations. Patients with severe CONUT scores had shorter survival durations than those with moderate, mild, and normal scores (**Figure F**). However, no statistically significant association was observed among patients with a history of Auto-PBSCT between CONUT scores and survival durations (**Figure E**). Patients with a history of Auto-PBSCT exhibited a statistically significant relationship between GNRI scores and survival durations. Patients in the low-risk group had shorter survival durations than those in the no risk and severe/moderate-risk groups. No statistically significant association was found between survival durations and GNRI scores among patients without a history of Auto-PBSCT (**Figure G and H**).

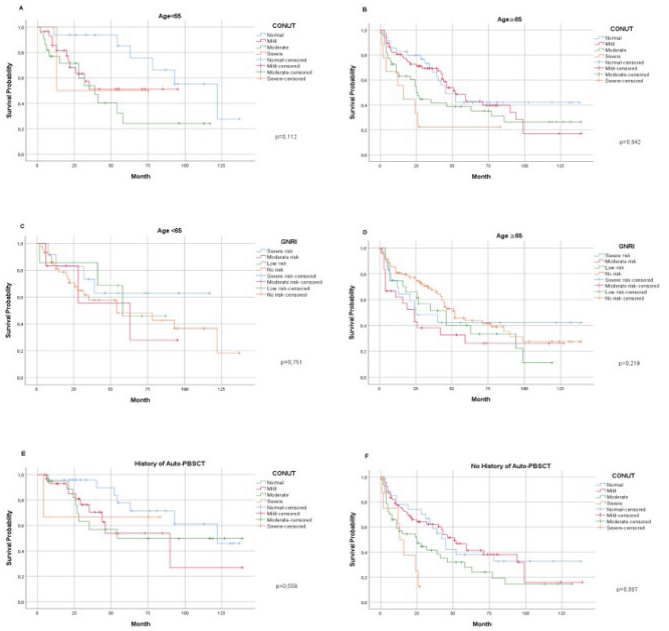

**Figure.** (A)The Kaplan-Meier curve estimates for overall survival (OS) among patients younger than 65 years indicate that the median OS for those with a normal CONUT score was 122 months. In contrast, patients with moderate and severe CONUT scores had a median OS of 39 and 13 months, respectively. (B) For patients aged 65 and older, the median OS was 45 months for those with a normal CONUT score, 52 months for those with a mild CONUT score, 25 months for those with a moderate CONUT score, and 16 months for those with a severe CONUT score. (C) In the cohort under 65, the median OS was 63 months in moderate GNRI score patients; individuals with a low-risk GNRI score had a median OS of 58 months, while those with no risk had a median OS of 54 months. (D) Among patients aged 65 and older, the median OS was 24 months for those with severe GNRI risk, 24 months for those with moderate GNRI risk, 46 months for low GNRI risk, and 52 months for no risk GNRI. (E) For patients with a history of Auto-PBSCT, the median OS was 122 months for those with a normal CONUT score, 90 months for those with a mild CONUT score, and 54 months for those with a moderate CONUT score. (F) In contrast, for patients with no history of Auto-PBSCT, the median OS was 45 months for those with a normal CONUT score, 51 months for those with a mild CONUT score, 25 months for those with a moderate CONUT score, and 13 months for those with a severe CONUT score. (G) Among patients with a history of Auto-PBSCT, the median OS was 63 months for those with moderate GNRI scores, 35 months for low-risk GNRI scores, and 122 months for those with no risk. (H) Additionally, in patients with no history of Auto-PBSCT, the median OS was 25 months for those with severe GNRI scores, 19 months for those with moderate GNRI scores, 58 months for those with low-risk GNRI scores, and 43 months for those with no risk

## DISCUSSION

Malnutrition is a clinical condition that often goes unnoticed in clinics but, if left untreated, significantly increases morbidity and mortality risks, especially in the elderly population.[27] Those with chronic illnesses, organ transplant recipients, oncology patients, individuals requiring palliative care, the elderly, individuals in intensive care, and those who have undergone major surgery are recognized as high-risk groups for malnutrition.[28] Malnutrition is more commonly observed in elderly cancer patients undergoing chemotherapy and radiotherapy. Numerous studies have demonstrated that scoring systems such as CONUT and GNRI can monitor nutritional status and predict prognosis and mortality in chronic and malignant diseases.[29-31]

Multiple myeloma can occur in adults across a wide age range; however, it is most commonly seen in older individuals. Deaths associated with MM are most frequently observed in patients aged 65 and older.[32] This highlights the increasing risk of the disease with age and underscores the importance of managing and treating this elderly population effectively.[33] In recent years, the introduction of novel anti-myeloma agents has notably extended overall survival in patients with multiple myeloma. Despite these advancements, factors such as biological and genetic characteristics, along with complications arising from treatment, may affect individual responses to therapy. Therefore, improving treatment outcomes in MM patients necessitates a focus on minimizing therapy-related adverse effects.[34]

In this context, regular evaluation of patients' nutritional status and provision of nutritional support as needed are critical for optimizing management outcomes in these patients. The CONUT score has emerged as a significant prognostic indicator for patients with MM. Numerous studies have demonstrated that a higher CONUT score is associated with poorer OS in MM patients.[35-37] The CONUT score, which incorporates serum albumin, total cholesterol, and absolute lymphocyte count, reflects both nutritional and inflammatory status in hematological malignancies.[38] As an immune-nutritional index, the CONUT score offers a convenient and accessible method for predicting MM patient outcomes, potentially guiding treatment strategies, and improving clinical management.[37,38]

Lu and Li;[39] conducted a meta-analysis investigating the role of the CONUT score in hematologic malignancies. The study reviewed 23 articles and found that the CONUT score independently predicts poor OS in patients with hematologic malignancies. Additionally, they found that a high CONUT score is linked to a lower progression-free survival (PFS). These results indicate that nutritional status plays a crucial role in the prognosis of hematologic malignancies, underscoring the importance of the CONUT score in the management of these patients.

The GNRI has emerged as a valuable prognostic tool in various hematologic malignancies. Studies have shown that a low GNRI score is associated with poorer OS and PFS in patients with hematologic malignancies.[20] In multiple myeloma, the International Myeloma Working Group score, which incorporates elements similar to GNRI, has demonstrated substantial prognostic value for functional decline and OS.[40] In patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) treated with azacitidine, a low GNRI was independently linked to increased early mortality and shorter overall survival (OS). While the GNRI was initially validated in cardiovascular patients, its relevance in hematologic malignancies emphasizes its potential as a straightforward and effective tool for evaluating nutritional risk and predicting outcomes in these patient groups.[41]

Academic studies on CONUT score in MM patients provide valuable insights into assessing patients' nutritional status and predicting prognosis. These studies typically focus on examining the impact of patients' nutritional status on the course of MM and their response to treatment. This study has demonstrated that CONUT and GNRI scores, indicators of nutritional status in patients with MM, may serve as independent prognostic factors for OS. The findings indicate that, especially in MM patients aged 65 years and older, the CONUT score is consistent with its role in other cancer types, showing malnutrition as a marker of poor prognosis. Additionally, in patients without a history of auto-PBSCT, the CONUT score was associated with OS. On the other hand, the GNRI score was correlated with response to first-line treatment and OS in patients with a history of Auto-PBSCT. These findings underscore the significant role nutritional status assessments can play in managing treatment and prognosis in MM patients.

## CONCLUSION

This study has helped us understand the impact of nutritional parameters on mortality in MM patients. Our findings suggest improving patients' nutritional status can positively affect treatment outcomes and survival. Scoring systems such as CONUT and GNRI are essential tools for assessing nutritional status and plan treatments for MM patients. Academic research in this field enhances our understanding of the effectiveness and significance of these scores in clinical practice.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of the Sivas Cumhuriyet University Non-interventional Clinical Researches Ethics Committee (Date: 18.01.2024, Decision No: 2024-01/08).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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